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DATA EVALUATION RECORD

008139

I. SUMMARY

MRID (Acc.) No.: 412552-26
ID No.: 7078-RT
RD Record No.: 253,112
Caswell No.: 623C (129017)
Project No.: 0-0339

Study Type: Mutagenicity - Chromosome aberration in rats (bone marrow)

Chemical: CIDEX OPA Antimicrobial (ortho-phthalaldehyde)

Sponsor: Surgikos, Inc., Arlington, TX

Testing Facility: Microbiological Associates (M/A)
Bethesda, MD

Title of Report: Acute in vivo Cytogenetics Assay in Rats.

Author: Donald L. Putnam

Study Number: (M/A) T824I.105007

Date of Issue: April 27, 1989

TB Conclusions:

Although severely toxic to Sprague-Dawley rats administered single oral doses of test article up to 50 to 100 mg/kg, no evidence was presented that a cytotoxic and/or effective concentration reached the target, bone marrow cells.

Classification (Core-Grade:

UNACCEPTABLE in its present form.

II. DETAILED REVIEW

A. Test Material - 913-12 (ortho-phthalaldehyde, OPA)

Description: Pale yellow crystalline solid
Batch (Lot): 861-650
Purity (%): 99.7
Solvent/Carrier/Diluent: Water (DW)

B. Test Organism - Rodent

Species: Rat
Strain: Sprague-Dawley
Age: 6 to 8 weeks
Weights - Males: 185 to 235 g
Females: 139 to 181 g
Source: Harlan Sprague-Dawley, Frederick, MD

C. Study Design (Protocol) - This study was designed to asses the clastogenic (chromosome-breaking) potential of OPA when administered once by oral gavage to male and female rats according to an enclosed protocol based upon recognized (published) procedures and methods.

Statements of both Quality Assurance measures (inspections/audits) as well as adherence to Good Laboratory Practice were provided.

D. Procedures/Methods of Analysis - Groups of rats (5/sex/group) were administered test article once by oral gavage at doses of 0 (DW vehicle), 10, 50, and 100 mg/kg, and sacrificed 7, 24, or 48 hours later, following IP injection of the mitotic-arresting alkaloid, colchicine (1 mg/kg). Two additional groups of rats (5/sex) were dosed once orally with the mutagen, cyclophosphamide (CP, 25 mg/kg), and sacrificed 24 hours later.

Immediately following sacrifice, bone marrow was aspirated from both femurs of each animal and prepared for slide microscopic examination by conventional cytological techniques. Giemsa-stained coded slides were scored (3 slides per animal each containing 50 metaphases) for chromatid and chromosome aberrations (both simple and complex), and a mitotic index (MI = cells in metaphase per 500 cells counted) recorded for each animal.

All data were analyzed by Fisher's Exact Test (to compare percentage of damaged cells between treated and solvent groups), and the Cochran-Armitage trend test applied to determine any evidence of a dose response. To be considered valid for analysis, the percentage of cells in the negative control with aberrations must not

exceed 4 percent, and the aberration index among positive controls must be statistically increased over the solvent value.

E. Results - Reductions in body weight over background (6.4% in males, 4.3% in females) were recorded in females receiving 10 mg/kg OPA (-2.5%), in males receiving 50 mg/kg (-12.3%), and in both sexes receiving 100 mg/kg (-13.4%/-11.2%, males/females) (Report Table 1). In addition, adverse clinical signs (lethargy and/or labored breathing, prostration, nasal and/or oral secretion, piloerection) were observed at all doses: At 10 mg/kg, 2 animals; at 50 and 100 mg/kg, "the majority" of rats.* A total of 14 animals died during the study: at 50 mg/kg, 1/15 males and 1/15 females; at 100 mg/kg, 5/20 males and 7/20 females.

At no dosage or sample period, however, did the percentage of damaged metaphases significantly exceed solvent control values ($p > 0.05$, Fisher's), whereas the CP group recorded a large increase ($p < 0.01$) in cells containing one or more (complex) chromosomal aberrations (Report Tables 2 and 3 attached to this DER; based upon number and types of aberrations on individual slides from each animal collected as Report Tables 4 through 9, not displayed here).

Hence, the investigator concluded that the test article, OPA, was negative for inducing chromosome damage in bone marrow cells of S-D rats dosed acutely up to lethal levels.

F. TB Evaluation - UNACCEPTABLE. That the test article (OPA technical) is severely toxic to rats at single oral doses of 50 mg/kg and above has been amply demonstrated here. However, this type of assay was meant to test for potential cytogenetic damage in bone marrow cells (a recognized target organ for mutagenicity evaluation), and not as an abbreviated oral toxicity test. No evidence is presented in the Final Report that the chemical is absorbed from the gastrointestinal tract and transported to the target in sufficient concentration to affect bone marrow cells, or even erythropoiesis (cf., adverse or cytotoxic effects). Such acceptable evidence could include radioactive tracer studies, alterations (usually delays) in cell cycle kinetics, or

*No detailed breakdown was provided in the Final Report.

changes in ratios of developing erythrocytes. This study can be upgraded if cytotoxic evidence is available and submitted for review.

[NB: An adequate test for the potential of OPA to cause cytogenetic damage in vivo is all the more necessary since concurrent in vitro cytogenetic assays conducted by the same laboratory have demonstrated positive results (T8241.334 and T8241.337).]

Attachments (Summary Data Tables)

ATTACHMENT I

Summary Data Tables

Page _____ is not included in this copy.

Pages 6 through 8 are not included in this copy.

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